REMARKS

Specification Amendments

The sequence listing paragraph in the specification has been amended merely to update the information in the revised sequence listing, submitted herewith.

Claim Amendments

In order to advance prosecution, Applicants have amended claim 1 and dependent claims 3, 10, 11-17, 18-21, 30 and 31 and have canceled claims 2, 4-9, and 22-29. Specifically, claim 1 has been amended to recite a double stranded nucleic acid molecule about 18 to about 27 nucleotides in length comprising SEQ ID NO: 305. Support can be found in the specification at, for example, pages 8, 9, 11, 16, 17, 34, 55, 74, and 79, and Tables I and II. Claims 3, 10, 11-17, 18-21, 30 and 31 have been amended to recite a double stranded nucleic acid molecule. Support for the amendment can be found throughout the specification.

Amendments to the claims are made without prejudice and do not constitute amendments to overcome any prior art or other statutory rejections and are fully supported by the specification as filed. Additionally, these amendments are not an admission regarding the patentability of subject matter of the canceled or amended claims and should not be so construed. Applicant reserves the right to pursue the subject matter of the previously filed claims in this or in any other appropriate patent application. The amendments add no new matter and applicants respectfully request their entry.

The Sequence Listing

Applicants have enclosed a revised sequence listing and request its entry in place of the previously entered sequence listing. The revised sequence listing merely adds SEQ ID NO: 305 which sequence represents GenBank entry NM_000740.1. Support for SEQ ID NO: 305 can be found in Tables I and II and, for example, on pages 8, 9, 11, 16, 17, 55,

74, and 79. The version of NM_000740.1 appearing in the sequence listing as SEQ ID NO: 305 appeared in GenBank on October 31, 2000. The sequence listing adds no new matter and applicants respectfully request its entry into the specification.

Rejection of Claims 36-69 Under 35 U.S.C. § 112, first paragraph

Claims 1-31 stand rejected under 35 USC § 112, first paragraph, as allegedly failing to comply with the written description requirement. Claims 2, 4-9, and 22-29 have been canceled. Therefore, the rejection is moot as applied to these claims. Applicants respectfully traverse the rejection as it applies to claims 1, 3, 10, 11-17, 18-21, 30 and 31.

The Office Action asserts that the claims do not recite any sequence identifier relating to CHRM3, but rather recite a broad genus of CHRM3 sequences. The Office Action argues that the specification describes siNA molecules targeted to a single species of CHRM3 sequence and concludes that one of ordinary skill in the art could not make oligos to any CHRM3 sequence without knowledge of the sequence. Applicants strongly disagree with the Office's argument.. Applicants teach the sequence of several CHRM3 sequences (see CHRM3 sequences referred to by Genbank Accession numbers listed in Table I) including other CHRM3 encoding sequences, such as other CHRM3 isoforms, mutant CHRM3 genes, splice variants of CHRM3 genes, and CHRM3 gene polymorphisms (see pages 8, 10, and 54, as well as Table I). Based on the detailed teachings in the specification, one skilled in the art would be able to make siNA molecules to the various CHRM3 sequences. However, in order to advance prosecution, claim 1 has been amended to recite double stranded nucleic acid molecules having complementarity to human CHRM3 RNA comprising SEQ ID NO: 305 (Isoform NM_000740.1).

Applicant respectfully requests withdrawal of the 35 U.S.C. §112, first paragraph, rejection.

Priority

The Office Action alleges that the instant application is not entitled to priority to International Patent Application PCT/US03/05028 and U.S. Provisional Applications 60/358,580, 60/363,124, 60/386,782, 60/406,784, 60/408,378, 60/409,293, and 60/440,129. The Applicant respectfully disagrees.

The Office specifically alleges that the instant application does not receive the benefit of the priority documents because the recited target, CHRM3, is not disclosed in the specification or claims of the priority applications. However, contrary to the Office's allegation, the pending claims find support in, *inter alia*, the 60/363,124 application (the '124 application), filed March 11, 2002. For example, the '124 application teaches the recited target, CHRM3, in Table I. In addition, amended claim 1 finds support for chemically synthesized double-stranded nucleic acid molecule at p. 3, lines 15-17; p. 32, lines 11-12; p. 35, lines 29-30, and p. 60, line 20; complementarity between the first and second strands at p. 12, lines 4-7, p. 19, lines 11-14, p. 20, lines 16-20, p. 21, lines 3-6, and p. 25, lines 17-29; one strand having between 18-27 nucleotides complementary to CHRM3 RNA at p. 18, lines 1-5, p. 12, line 6, p. 409, entry in Table III for GenBank Accession No. NM_000740; and at least one sugar modification at p. 6, line 19 to page 8, line 10, and p. 36, lines 2, 13, and 19-31.

Support for the dependent claims can also be found in, *inter alia*, the '124 application:

Claim	Support
3	One or more ribonucleotides: p. 15, lines 3-9
10	Sense strand connected to antisense strand via linker molecule: p. 19, lines 20-21, 25, 28, p. 20 line 15, p. 38 lines 17-29
11	Polynucleotide linker: p 12, lines 13-26, p. 38, lines 18-29
12	Non-nucleotide linker: p 12, lines 13-26
13	One or more pyrimidine nucleotides present in sense strand are 2'-O-

Claim	Support
	methyl pyrimidine nucleotides: p. 10, lines 13, 27, p. 11, lines 8, 22
14	One or more purine nucleotides present in the sense strand are 2'-deoxy purine nucleotides: p. 6, lines 14-15
15	One or more pyrimidine nucleotides present in the sense strand are 2'-deoxy-2'-fluoro pyrimidine nucleotides: p. 10, lines 13-14, 27, p. 11, lines 8-9, 22
16	Sense strand includes a terminal cap moiety at the 5'-end, the 3'-end, or both of the 5' and 3' ends of the sense strand: p. 10, lines 6-7, 20-21, p. 40, lines 1-18
17	Terminal cap moiety is inverted deoxy abasic moiety: p. 5, line 16, p. 14, lines 10-13, p. 40, lines 4-18.
18	One or more pyrimidine nucleotides present in the antisense strand are 2'-deoxy-2'-fluoro pyrimidine nucleotides: p. 10, lines 13-14, 27, p. 11, lines 8-9, 22
19	One or more purine nucleotides in antisense strand are 2'-O-methyl purine nucleotides: p. 6, lines 14-15
20	One or more purine nucleotides present in the antisense strand are 2'-deoxy purine nucleotides: p. 6, lines 14-15
21	Terminal phosphorothioate internucleotide linkage at 3' end of antisense strand: p. 9, lines 24-25
30	Terminal phosphate group: p. 8, line 26 to p. 9, line 13
31	Composition comprising the double stranded nucleic acid molecule in a pharmaceutically acceptable carrier or diluent: p. 18, lines 15-19

Therefore, the instant application is entitled to.the filing date of Provisional Application 60/363,124, i.e., a priority date of at least March 11, 2002.

Rejection of Claims 36-69 Under 35 U.S.C. § 103(a)

Claims 1-31 stand rejected as allegedly obvious over Elbashir *et al.*, 2001, EMBO J., 20:6877-6888, in view of Forsythe *et al.*, 2002, A. J. Respir. Cell Mol. Biol., 26:298-305, *Sato et al.*, 1999, Neuroscience Letters, 266:17-20, Tuschl *et al.* (WO 02/44321), Matulic Adamic *et al.* (U.S. 5,998,203) and Morrissey *et al.* (U.S. Publ. No. 2003/0206887). Claims 2, 4-9, and 22-29 have been canceled. Therefore, the rejection is moot as applied to these claims. Applicants respectfully traverse the rejection as it applies to claims 1, 3, 10, 11-17, 18-21, 30 and 31.

Initially, for the reasons stated above, the instant application has an earlier priority date than Morrissey *et al.* U.S. Publ. No. 2003/0206887, which is thus not a proper prior art reference.

The amended claims recite chemically synthesized double-stranded nucleic acid molecules comprising a sense strand and an antisense strand. Each strand of the double stranded nucleic acid molecule is 18 to 27 nucleotides in length. The antisense strand has complementarity to the CHRM3 RNA comprising SEQ ID NO:305 and the sense strand has complementarity to the antisense strand. The double stranded nucleic acid molecule molecule has at least one chemically modified nucleotide in the sense strand and the antisense strand.

Applicants submit that the Office Action has not established a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the references, when combined must teach or suggest all the claim limitations. *See* MPEP §2143.

First, the cited references do not teach alone or in combination all of the claim elements of the claimed invention, namely:

1. A chemically modified double-stranded nucleic acid molecule comprising a sense strand and an antisense strand;

2. wherein each strand of the double stranded nucleic acid molecule is 18 to 27 nucleotides in length;

3. wherein the antisense strand of the double stranded nucleic acid molecule comprises a nucleotide sequence that is complementary to a nucleotide sequence of said CHRM3 RNA comprising SEQ ID NO:305; and the sense strand is complementary to the antisense strand; and

4. wherein the double stranded nucleic acid molecule comprises at least one chemically modified nucleotide in said sense strand and said antisense strand of said double stranded nucleic acid molecule.

Elbashir and Tuschl teach siRNA technology generally, but fail to teach, mention, or suggest double stranded nucleic acid molecules targeting CHRM3 RNA comprising SEQ ID NO: 305.

Forsythe *et al.* fails to cure the deficiencies of Elbashire and Tuschl. Forsythe *et al* merely teach the cDNA encoding the human m3 muscarinic receptor gene.

Likewise, Sato *et al.* fails to cure the deficiencies of Elbashire and Tuschl. Sato *et al.* teach that muscarinic receptor subtype m3 is present on various blood cells, including peripheral lymphocytes, and that muscarinic receptor agonists modulate the functions of lymphocytes. Sato *et al.* does not teach or suggest that overexpression of CHRM3 could be controlled with double stranded nucleic acid molecules and certainly provides no teachings regarding double stranded nucleic acid molecules targeting CHRM3 RNA comprising SEQ ID NO: 305.

Matulic-Adamic is directed to general ribozyme technology and provides no teachings whatsoever regarding targeting CHRM3 RNA or, in particular, using double stranded nucleic acid molecules to target CHRM3 RNA comprising SEQ ID NO: 305. In fact, Matulic-Adamic is not art the ordinary artisan would consider in making the claimed invention; it is non-analogous art. In order to rely on a reference as a basis for rejection of an applicant's

invention, the reference must either be in the field of applicant's endeavor or, if not, then it must be reasonably pertinent to the particular problem with which the inventor was concerned." In re Oetiker, 977 F.2d 1443, 1446, 24 U.S.P.Q.2d 1443, 1445 (Fed. Cir. 1992).

Matulic-Adamic is simply not pertinent to the problem addressed by the presently claimed compounds, which is to provide double stranded nucleic acid molecules targeting CHRM3 RNA comprising SEQ ID NO: 305. Matulic-Adamic teach ribozymes, which were known to modify RNA by a mechanism completely different and unrelated to RNAi. Despite the voluminous literature in the RNAi field, the applicants are unaware of a single instance in which a teaching regarding ribozymes has provided any insight into RNAi or been used in the study and development of double-stranded nucleic molecules that induce cleavage of target RNA by RNAi. Matulic-Adamic is simply not a reference that would have commended itself to one of ordinary skill in the art in the development of the presently claimed molecules or those of Elbashir or Tuschl, which are not ribozymes.

However, for the sake of argument, even if one skilled in the art would have considered Matulic-Adamic, this patent fails to teach, mention, or suggest double stranded nucleic acid molecules targeting CHRM3 RNA comprising SEQ ID NO: 305 and therefore does not overcome the deficiencies of Elbashir even in combination with the other cited references.

Second, contrary to the Office's allegation, there is no suggestion or motivation to combine the cited references. There is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings. There must be some reason, suggestion, or motivation found in the cited references whereby a person of ordinary skill in the field of the invention would make the substitutions required. That knowledge cannot come from the applicants' disclosure of the invention itself. *Diversitech Corp. v. Century Steps, Inc.*, 7 U.S.P.Q.2d 1315,1318 (Fed. Cir. 1988); *In re Geiger*, 2 U.S.P.Q.2d 1276,

1278 (Fed. Cir. 1987); *Interconnect Planning Corp. v. Feil*, 227 U.S.P.Q. 543, 551 (Fed. Cir. 1985).

An examiner can satisfy burden of the obviousness in light of combination "only by showing some objective teaching [leading to the combination]." *See, In re Fritch*, 972 F.2d 1260, 1265, 23 U.S.P.Q.2d 1780, 1783 (Fed. Cir. 1992). Evidence of the teaching or suggestion is "essential" to avoid hindsight. *In re Fine*, 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596, 1600 (Fed. Cir.1988). Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability–the essence of hindsight. *See, e.g., Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1138, 227 U.S.P.Q. 543, 547 (Fed. Cir. 1985). "Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references." *In re Dance*, 160 F.3d 1339, 1343, 48 U.S.P.Q.2d 1635, 1637 (Fed. Cir. 1998). The need for specificity is important. *See, e.g., In re Kotzab*, 217 F.3d 1365, 1371, 55 U.S.P.Q.2d 1313, 1317(Fed. Cir. 2000) ("particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed").

While a suggestion need not be express in the prior art, it must be clear and particular; broad conclusory statements about the teachings of multiple references is insufficient. *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 56 U.S.P.Q.2d 1456, 1459 (Fed. Cir. 2000). The mere identification of a target (Sato) and a general mechanism for suppressing expression (Elbashir and Tuschl) without more is not the type of particularized suggestion necessary to sustain an obviousness rejection. The art must suggest the combination; it cannot come from the applicant's disclosure.[1]

[1] Indeed, the Board of Appeals made this very point in a non-precedential opinion (copy enclosed), holding that one publication's teaching of

a) general rules for the design of new RNA enzymes capable of highly specific RNA cleavage,
b) successful tests of these RNA against target sequences, and

Contrary to the Office's allegation, none of the cited references that disclose the CHRM3 target would motivate one of skill in the art to target CHRM3 with double stranded nucleic acid molecules. The references that describe CHRM3 gene (Forsythe and Sato) fail to teach or suggest any down-regulation of a CHRM3 gene and do not teach or suggest any nucleic acid or RNA sequence comprising SEQ ID NO: 305 as a target for expression based modulation. As such, there would be no motivation to combine Forsythe and Sato with Elbashir as would be required to practice the present invention.

Moreover, even if for the sake of argument there was a motivation to combine, the cited references do not provide a reasonable expectation of success. The existence or lack of a reasonable expectation of success is assessed from the perspective of a person of ordinary skill in the art at the time the invention was made. *See Micro Chem. Inc. v. Great Plains Chem. Co.*, 103 F.3d 1538, 1547, 41 U.S.P.Q.2d 1236, 1245 (Fed. Cir. 1997). The inventors' ultimate success is irrelevant to whether one of ordinary skill in the art, at the time the invention was made, would have reasonably expected success. *See Standard Oil Co. v. American Cyanamid Co*, 774 F.2d 448, 454, 227 U.S.P.Q. 293, 297 (Fed. Cir. 1985). It is impermissible to use hindsight. That is, using the inventors' success as evidence that the success would have been expected. *See In re Kotzab*, 217 F.3d 1365, 1369, 55 U.S.P.Q.2d 1313, 1316(Fed. Cir. 2000).

The priority date of the application is at least March 11, 2002. Therefore, as of March 11, 2002, it must be determined if one of ordinary skill in the art had a reasonable expectation of success in making a chemically modified double-stranded nucleic acid molecule comprising a sense strand and an antisense strand, wherein each strand of the double stranded nucleic acid molecule is 18 to 27 nucleotides in length; wherein the antisense strand of the double stranded nucleic acid molecule comprises a nucleotide sequence that is complementary to a nucleotide sequence of said CHRM3 RNA comprising

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c) the conclusion that provided that transcribed sequences of a gene are known it should be possible to target one or more ribozymes against specific RNA transcripts,

and a second publication's teaching of the TGF-β sequence did not establish a *prima facie* case of obviousness of a claim to an anti-TGF-β ribozyme absent a suggestion or motivation found in the prior art to combine the references. The Board warned that the knowledge cannot come from the applicant's disclosure.

SEQ ID NO: 305 and the sense strand is complementary to the antisense strand; and wherein the double stranded nucleic acid molecule comprises at least one chemically modified nucleotide in said sense strand and said antisense strand of said double stranded nucleic acid molecule.

In 2001 one of ordinary skill in the art knew:

1. That siRNA technology existed. *See*, Elbashir and Tuschl
2. The sequence for cDNA encoding the human m3 muscarinic receptor gene. *See*, Forsythe;
3. That chemical modifications could be made to ribozymes. *See*, Matulic-Adamic.

One of ordinary skill in the art, as of March 11, 2002, would not have had a reasonable expectation of success of making a chemically modified double stranded nucleic acid molecule comprising a sense strand and an antisense strand that is complementary to CHRM3 RNA having SEQ ID NO: 305, wherein the double stranded nucleic acid molecule comprises at least one chemically modified nucleotide in both the sense strand and the antisense strand. The cited references merely demonstrate that double stranded nucleic acid technology existed, that the cDNA sequence of the human m3 muscarinic receptor gene was known, and that chemical modifications could be made to ribozymes which are distinct from the double stranded nucleic acid molecules of the invention. In the absence of any teaching whatsoever of a double-stranded nucleic acid molecule as presently claimed, one skilled in the art would have no reasonable expectation of success of making such molecules.

For the reasons set forth above, Elbashir, in view of Forsythe, Sato, Tuschl, and Matulic-Adamic does not teach or suggest making a double-stranded short interfering molecule targeting a CHRM3 RNA having SEQ ID NO:305 with a reasonable expectation of success and thus does not render the present invention obvious. Accordingly, Applicant respectfully requests withdrawal of the 35 U.S.C. § 103(a) rejection.

Obviousness-type Double Patenting Rejection

Claims 1-31 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-31 of copending Application Serial No. 10/919,866.

Without conceding to the merits of the Office's arguments, and subject to Applicant's further consideration of the subject matter of allowed claims, Applicant will consider filing a terminal disclaimer over Application Serial No. 10/919,866 upon issuance of the patent.

Conclusion

In view of the foregoing amendments and remarks, the applicant submits that the claims are in condition for allowance, which is respectfully solicited. If the examiner believes a teleconference will advance prosecution, she is encouraged to contact the undersigned as indicated below.

Respectfully submitted,

Date: November 8, 2005

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